REMARKS

Reconsideration and withdrawal of the rejections of the claims in view of the amendments and remarks presented herein is respectfully requested. Claims 1-35, 39-46, 49-61, 63-71 and 73-78 are canceled without prejudice or disclaimer, and solely to advance prosecution of the present application. Claims 36-38, 47-48, 62, and 72 are now pending in this application.

Applicants request that the Examiner note that the Attorney docket number on this matter has changed to 17023-012001.

The 35 U.S.C. §112 Rejection of the Claims

The Examiner rejected claims 36-37, 39-48 and 62-78 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. In particular, the Examiner asserts that Applicants have not reduced to practice all soluble lysosomal enzymes or "any naturally secreted proteins . . . nuclear proteins and cytoplasmic proteins," and further that the specification does not adequately describe "the essential structural feature that provides the recited function of any and all soluble lysosomal enzymes, naturally secreted proteins, . . . nuclear proteins and cytoplasmic proteins" (page 5 of the Office Action).

Claims 39-46, 63-71 and 73-78 have been cancelled. Insofar as this rejection is retained with respect to the currently pending claims, it is respectfully traversed. As amended, the claims are directed to a polypeptide comprising a soluble lysosomal enzyme operably linked to a PTD, wherein the polypeptide is biologically active. Therefore, all the pending claims recite a soluble lysosomal enzyme.

Page 5 of the Office Action states that a "soluble lysosomal enzyme" encompasses any molecule with the functional activity of acid hydrolyzing complex chemicals in the body. Applicants respectfully disagree with this definition. As used in the present specification, a lysosomal enzyme is an enzyme whose functional biological activity occurs in a lysosome. The lysosomal enzymes are trafficked into the lysosome naturally as a consequence of the sugars on

the enzymes. The application discloses that lysosomal storage diseases, a number of which are disclosed at page 4, line 26-page 5, line 1, are genetic diseases caused by the deficiency of lysosomal enzymes (page 2, line 21-page 3, line 6), which are proteins involved in lysosomal biogenesis (see, Miekle *et al.*, incorporated by reference at page 2, line 26 of the present specification). Further, lysosomal enzymes are known in the art to be hydrolases involved in the catabolism of macromolecules (see Caillaud and Poenaru, *Biomed. and Pharmacother.*, 54:505-512 (2000). Further, as of the effective filing date of the present application, the art worker was aware of the particular types of lysosomal enzymes responsible for lysosomal storage diseases. For example, the lysosomal storage disease mucopolysaccharidosis type VII, also known as Sly syndrome, is caused by a deficiency in ß-glucuronidase activity (see Ghodsi *et al.*, of record, and O'Connor *et al.*, which is incorporated by reference at page 21, line 20 of Applicants' specification). In addition, the Examiner's attention is directed to Table 1 of Caillaud and Poenaru, wherein different types of lysosomal diseases and the responsible enzymes for each are disclosed. Thus, the specification has provided a written description of many soluble lysosomal enzymes.

It appears that the Examiner is equating an actual reduction to practice with adequate written description. Actual reduction to practice of all species included in a genus is not legally required in order for the genus to be adequately described. As discussed above, one of skill in the art would be aware of the known soluble lysosomal enzymes. This information, in conjunction with the teachings of, and the motivation provided by, the present specification would provide one of ordinary skill in the art an adequate written description of the invention. What is conventional or well known to one of ordinary skill in the art need not disclose in detail. M.P.E.P. § 2163.II.A.3(a) (*citing Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986)).

Thus, adequate description of the subject matter of the pending claims is either specifically taught by the specification and/or was known by those having skill in the art at the time the application was filed. Therefore, Applicants respectfully request that this rejection under 35 U.S.C. § 112, first paragraph (written description) be withdrawn.

The 35 U.S.C. §102(b) Rejection of the Claims

The Examiner rejected claims 36, 39, 45, 47, 48, 62, 63, 65-67, 70-71, 76 and 78 under 35 U.S.C. § 102(b) as being anticipated by Schwarze *et al.*, *Science*, 285:1569-1572 (1999). The cancellation of claims 39, 45, 63, 65-67, 70-71, 76 and 78 renders this rejection of claims 39, 45, 63, 65-67, 70-71, 76 and 78 moot. At this rejection may be maintained with respect to the pending claims it is respectfully traversed.

The standard for anticipation is one of strict identity, and to anticipate a claim for a patent a single prior art source must contain all its elements. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q.2d 90 (Fed. Cir. 1986); *In re Dillon*, 16 U.S.P.Q.2d 1987 (Fed. Cir. 1990). Furthermore, there must be no difference between the claimed invention and the disclosure, as viewed by a person of ordinary skill in the art. *Scripps Clinic & Res. Found. v. Genentech, Inc.*, 18 U.S.P.Q.2d 1001 (Fed. Cir. 1991).

As amended, the claims of the present invention are directed to polypeptides comprising a soluble lysosomal enzyme, *e.g.*, a soluble lysosomal storage enzyme, fused to a protein transduction domain (PTD).

The Examiner is urged to consider that lysosomes are eukaryotic organelles and are not found in prokaryotes. *See*, for example, Keeton, *Biological Science*, W.W. Norton and Co., New York (3rd edition, 1980) pages 109, 117-118 and 120-121. Pages 109, 117-118 and 120-121 are from Chapter 3, "Cells: Units of Structure and Function." In particular, at page 109, under the heading "Lysosomes," it is disclosed that lysosomes are "membrane-enclosed bodies . . . that . . . function as storage vesicles . . . for hydrolytic enzymes." Pages 117-118, under the heading "Eucaryotic vs. Procaryotic Cells," disclose that a "typical" eukaryotic cell contains a lysosome (*see* especially Figure 3.43 on page 118). Pages 120-121, under the heading "Procaryotic Cells" disclose that procaryotic cells "lack most of the cytoplasmic organelles present in eukaryotic cells." In particular, prokaryotic cells such as *E. coli* lack lysosomes. A soluble lysosomal enzyme, as recited by the present claims, is a particular type of protein generated by a lysosome, an organelle not found in procaryotic cells. Therefore, proteins derived from procaryotic organisms are by definition not lysosomal enzymes.

It should further be noted that there are many known β-galactosidase molecules; there is not just one β-galactosidase. Different organisms generate different types of β-galactosidase. While these enzymes all have β-galactosidase activity, i.e., they catalyze the hydrolysis of terminal non-reducing β-D-galactose residues in β-D-galactosides, they can vary considerably in their other functional and/or structural characteristics. For example, *E. coli* β-galactosidase is not a secreted protein, whereas mammalian β-galactosidase is secreted. (*See*, for example, Messageot *et al.*, (1998) *J. Biol Chem.*, 273(29):18594-19509, and Snyder *et al.* (2003) *Nature Med.* 9(2):231-235). Also, the pH optimum for *E. coli* β-galactosidase is distinct from the major lysosomal "acid" β-galactosidases. (Nielsen *et al.* (1983) *Proc. Natl. Acad. Sci. USA* 80(17):5198-5202).

Schwarze *et al.* disclose the preparation of a 120 kD *E. coli* β-galactosidase protein (*i.e.*, a prokaryotic protein) fused to PTD-TAT (Figures 2A and 2D; page 1570). On page 1571, Schwarze *et al.*, discussed employing a "116 kD β-galactosidase (β-gal) protein," and cited to Sanes *et al.*, *EMBO J.*, 5:3133-3342 (1986) and Rosenthal, Methods in Enzymology, 152:704-720(1987). Sanes *et al.* constructed a defective recombinant retrovirus containing the *E. coli* β-galactosidase (lacZ) gene (abstract). Rosenthal discuss using bacterial genes, such as bacterial β-galactosidase, as reporter genes (page 709-711). Thus, Schwarze *et al.* disclose a prokaryotic β-galactosidase fusion protein, which is not a lysosomal enzyme. Schwarze *et al.* further disclose the preparation of and transduction of murine cells with a 36 kD FITC-labeled TAT-human cycline-dependent kinase-2 (Cdk2-DN) or a 47 kD FITC-labeled yeast CAK1 (Cdk-activating kinase-1) (page 1571). These enzymes (Cdk2-DN and CAK1) are not lysosomal enzymes. Thus, Schwarze *et al.* do not teach or suggest a soluble lysosomal enzyme operably linked to a PTD fusion protein.

Further, Schwarze *et al.* teach that in their "protein transduction" method, the proteins are purified under denaturing conditions (page1570). In the present invention, the proteins are made *in situ*, *i.e.*, they are inherently made under biological conditions rather than under denaturing conditions.

Therefore, Schwarze *et al.* do not anticipate the presently claimed invention. Thus, because the cited art does not anticipate the presently pending claims, withdrawal of the rejection under 35 U.S.C.§102(b) is respectfully requested.

The 35 U.S.C. §103(a) Rejection of the Claims

The Examiner rejected claims 36-48 and 62-78 under 35 U.S.C. § 103(a) as being unpatentable over Schwarze *et al.* in view of Ghodsi *et al.*, Exp. Neuro., 160:109-116 (1999) or Hum. Gene Therapy, 9:2331-2340 (1998). In particular, at page 3 of the Office Action, the Examiner asserts that because Schwarze *et al.* allegedly teach that over 50 proteins have been fused to TAT PTD, that the art worker would have found it obvious at the time the present application was filed to fuse any protein to TAT PTD. This rejection is respectfully traversed insofar as it is applied to the pending claims.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the cited reference itself or in the knowledge generally available to an art worker, to modify the reference so as to arrive at the claimed invention. Second, there must be a reasonable expectation of success, *i.e.*, that the invention would be operable. Finally, the prior art reference must teach or suggest all the claim limitations (M.P.E.P. § 2143). The teaching or suggestion to make the claimed invention and the reasonable expectation of success must both be found in the prior art, not in Applicants' disclosure (M.P.E.P. § 2143, citing with favor *In re Vaeck*, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991)).

As discussed above, Schwarze *et al.* do not teach or suggest the preparation of TAT fusion proteins containing soluble lysosomal enzymes, as recited by the pending claims. At page 1570, Schwarze *et al.* disclose that their protein transduction method has been used to transduce over 50 proteins, and in support cite the following: Nagahara *et al.*, *Nature Medicine*, 4:1449-1452 (1998); Ezhevsky *et al.*, *Proc. Natl. Acad. Sci. USA*, 94:10699-10704 (1997); Lissy *et al.*, *Immunity*, 8:57-65 (1998); Gius *et al.*, *Cancer Research*, 59:2577-2580 (1999); and Vocero-

Akbani *et al.*, *Methods in Enzymology*, 322:508-521 (2000). None of the proteins discussed in these articles, however, are soluble lysosomal enzymes.

Therefore, while Schwarze *et al.*, by referencing each of Nagahara *et al.*, Ezhevsky *et al.*, Lissy *et al.*, Gius *et al.* and Vocero-Akbani *et al.* may teach or suggest the preparation of fusion proteins containing TAT and a cell cycle regulatory protein, there is nothing in Schwarze *et al.* that would teach or suggest to one of ordinary skill in the art the preparation of a polypeptide comprising a soluble lysosomal enzyme operably linked to a PTD. Because the cited reference does not teach or suggest all the claim limitations as required by M.P.E.P. § 2143, the claims are not obvious over Schwarze *et al.* Therefore, it is respectfully submitted that a *prima facie* case of obviousness has not been established, and that the pending claims are not rendered obvious by Schwarze *et al.*

Neither of Ghodsi *et al.* (1998) or Ghodsi *et al.* (1999) remedy the deficiencies of Schwarze *et al.* Ghodsi *et al.* (1998) disclose the administration of Adβgluc into β-glucuronidase-deficient mice. Ghodsi *et al.* (1999) tested the hypothesis that mannitol-induced hyperosmolality would increase the distribution of β-glucuronidase in brain following gene transfer to ependymal cells. Ghodsi *et al.* (1999), at page 110. They used an adenovirus carrying either the β-glucuronidase expression construct or a nuclear-targeted *E. coli* β-galactosidase report construct. Ghodsi *et al.* (1999), at page 111. These references do not teach or suggest a protein operably linked to a PTD, as recited by the pending claims. Thus, the Ghodsi *et al.* references do not teach all the limitations of the present invention.

Regarding the combination of Schwarze *et al.* and Ghodsi *et al.*, Applicants assert that the cited art does not contain a suggestion or incentive that would have motivated the skilled artisan to modify the references. The Federal Circuit in *In re Sang Su Lee*, 61 U.S.P.Q.2d 1430-1436, 1433 (Fed. Cir. 2002) stated the following:

> The factual inquiry whether to combine references must be thorough and searching. . . . [i]t must be based on objective evidence of record. This precedent has been reinforced in myriad decisions, and cannot be dispensed with. See, *e.g.*, *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1124-25, 56 U.S.P.Q.2d 1456, 1459 (Fed. Cir. 2000) ("a showing of a suggestion, teaching, or motivation to combine the prior art references is an 'essential

> component of an obviousness holding'") (quoting C.R. Bard, Inc., v. M3 Systems, Inc., 157 F.3d 1340, 1352, 48 U.S.P.Q.2d 1225, 1232 (Fed. Cir. 1998)); *In re Dembiczak*, 175 F.3d 994, 999, 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999) ("Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references."); *In re Dance*, 160 F.3d 1339, 1343, 48 U.S.P.Q.2d 1635, 1637 (Fed. Cir. 1998) (there must be some motivation, suggestion, or teaching of the desirability of making the specific combination that was made by the applicant); *In re Fine*, 837 F.2d 1071, 1075, 5 U.S.P.Q.2d 1596, 1600 (Fed. Cir. 1988) ("'teachings of references can be combined *only* if there is some suggestion or incentive to do so.'") (emphasis in original) (quoting *ACS Hosp. Sys., Inc. v. Montefiore Hosp.*, 732 F.2d 1572, 1577, 221 U.S.P.Q. 929, 933 (Fed. Cir. 1984)).

The Examiner is urged to consider that there is no teaching in the cited references to prepare polypeptides comprising soluble lysosomal enzymes operably linked to a PTD based upon the teachings of the cited art. As discussed above, Schwarze *et al.* injected purified, denatured proteins into mice. The Ghodsi *et al.* articles discussed administering viral vectors into mice. Thus, Schwarze *et al.* were working with proteins, and the Ghodsi researchers were working with viral vectors. There is no teaching in the references themselves to modify their approaches.

Further, the Examiner states at the end of page 3 that the "*in situ* expression of the claimed fusion peptide in the brain of a patient is an intended usage of the claimed product as [*sic*] does not read any patentable weight into the claims." Applicants respectfully disagree with this statement. Schwarze *et al.* needed to purify their proteins under denaturing conditions (see, page 1570). Obviously, if a polypeptide is expressed from an expression vector located *in situ* in a brain cell of a patient, as recited by pending claim 72, it is not present in a denatured state as taught by Schwarze *et al.* Therefore, this element does add patentable weight to the claim.

Applicants respectfully submit that a *prima facie* case of obviousness has not been established. Withdrawal of the rejection under 35 U.S.C. § 103(a) is therefore respectfully requested.

Conclusion

Applicants respectfully submit that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicants' attorney at (612) 337-2540 to facilitate prosecution of this application.

Enclosed herewith is a Petition for a Three-Month Extension of Time. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 17 March 2004

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